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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,509	12/05/2003	Hong Zhang	ISPH-0803	9823
55389 7590 01/15/2009 KNOBBE, MARTENS, OLSON & BEAR, LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614				
EXAMINER ZARA, JANE J				
ART UNIT 1635		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/728,509

**Applicant(s)**

ZHANG ET AL.

**Examiner**

Jane Zara

**Art Unit**

1635

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-9 and 11-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 11-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-85/86)  
Paper No(s)/Mail Date 10-15-08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Individual Patent Application
- 6) ☒ Other: Seq. Alignment Data

### **DETAILED ACTION**

This Office action is in response to the communication filed 10-15-08.

Claims 1-9, 11-19 are pending in the instant application.

### ***Response to Arguments and Amendments***

Applicant's arguments with respect to claims 1-9, 11-14, 17 and 18 have been considered but are moot in view of the new ground(s) of rejection set forth below.

### **Withdrawn Rejections**

Any rejections not repeated in this Office action are hereby withdrawn.

### **New Rejections**

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 11 and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Diamond et al (WO 02/72130).

Diamond et al (WO 02/72130) teach a composition comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide between 12-30 nucleobases comprising at least 8 consecutive nucleobases of SEQ ID NO. 64, and which oligonucleotide is 100% complementary to SEQ ID NO. 17 (see Accession No. ABV73748, and example 1, page 16 of Diamond et al; see accompanying alignment data between Acc. No. ABV73748 and the instantly claimed SEQ ID NO. 64).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9, 11-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diamond et al (WO 02/72130) as applied to claims 1, 2, 11 and 13 above, in view of Korsmeyer (USPN 6,500,626) and further in view of Milner et al and McKay insofar as the claims are drawn to compositions and methods of inhibiting the expression of the BCL2-associated x protein in vitro comprising administration of a composition comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide between 12-30 nucleobases in length comprising at least 8 consecutive nucleobases of SEQ ID NO: 64 and which oligonucleotide is 100% complementary to SEQ ID NO. 17, which oligonucleotide comprises a phosphorothioate internucleotide linkage, a 2'-O-methoxyethyl sugar moiety and a 5'methyl-cytosine, and which is optionally a chimeric oligonucleotide, and which composition further comprises a colloidal dispersion system and gap segment consisting of ten linked deoxynucleotides, a 5' wing segment consisting of five linked nucleotides, a 3' wing segment consisting of five linked nucleotides, and which gap segment is between the 5' and 3' wings, and each wing comprises a 2'-O-methoxyethyl sugar and wherein each internucleoside linkage is a phosphorothioate linkage.

Diamond et al (WO 02/72130) is relied upon as cited in the 102 rejection above.

Diamond does not teach antisense oligonucleotides comprising phosphorothioate internucleotide linkages, 2'-O-methoxyethyl modified sugar moieties or 5-methyl cytosine nucleobases, nor chimeric antisense oligonucleotides, nor colloidal dispersion systems, gapmers.

Korsmeyer (6,500,626) teach the inhibition of expression of SEQ ID No. 17, encoding the BCL2-associated x protein, using antisense oligonucleotides (see col. 29 and col. 46, lines 54-56).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro, including the coding region, the 5', 3' untranslated regions, and stop codon regions of the target gene (See figure 1 on p 538 and figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach colloidal dispersion compositions comprising antisense oligonucleotides between 12 and 30 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and antisense oligonucleotides optionally design choices of modifications comprising 5' wing segments consisting of five linked nucleotides, 3' wing segments consisting of five linked nucleotides, and a gap segment between the 5' and 3' wings, wherein each wing comprises a 2'-O-methoxyethyl sugar and wherein each internucleoside linkage is a phosphorothioate linkage, and which antisense targets various regions of a target gene. McKay et al also teach the in vitro inhibition and screening of modulators (e.g. of various antisense oligonucleotides between 12-30 nucleobases that specifically hybridize with the target gene).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides between 12-30 nucleobases in length comprising at least 12 contiguous nucleobases of SEQ ID NO. 64 to inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein (BAX) in vitro, because Diamond teaches this antisense sequence, and Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro, including various regions of the target gene of interest, using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15).

It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of BCL2-associated x protein in vitro comprising the administration of antisense oligonucleotides between 12-30 nucleobases because Diamond teaches such an antisense oligonucleotide, and antisense of this size range, including the 20mer consisting of SEQ ID NO. 64, would have been a logical design choice for the target region previously disclosed by Diamond. Furthermore, antisense oligonucleotides of 20 nucleobases directed to a target gene region of known sequence (e.g. the well known Bax target gene sequence) were well known in the art for successfully targeting and inhibiting the expression of a known target gene, and Milner teaches methods of designing and assessing antisense oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro. One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 12-30 nucleobases which best target and

inhibit BCL2-associated x protein expression in order to study this target molecule's role in apoptosis, and its role in pathologies related to aberrant expression of BAX, including such conditions as Parkinson's, Alzheimer's.

One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 12-30 nucleobases) for the in vitro inhibition of BCL2-associated x protein expression, including the well known region targeted by SEQ ID NO. 64. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have expected that the delivery of modified antisense oligonucleotides to target cells harboring BCL2-associated x protein, which antisense specifically hybridize with the target nucleic acid encoding BCL2-associated x protein (e.g. of the 3' UTR of SEQ ID No. 17), would lead to inhibition of expression of BCL2-associated x protein in vitro.

Therefore, the invention as a whole would have obvious to one of ordinary skill in the art at the time the invention was made.



### ***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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**Jane Zara**

**1-13-09**

/Jane Zara/

Primary Examiner, Art Unit 1635